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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/516,705	12/02/2004	Takahito Hara	68138(46590)	1003

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EXAMINER	
BRISTOL, LYNN ANNE	

ART UNIT	PAPER NUMBER
1643	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/516,705	HARA ET AL.	
	Examiner	Art Unit	
	LYNN BRISTOL	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *4/16/10*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-11,13-64,73 and 78* is/are pending in the application.

4a) Of the above claim(s) *1-11 and 13-64* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *73 and 78* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *6/14/10* .
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-11, 13-64, 73 and 78 are all the pending claims in the application.

2. Claims 12, 71, 72 and 74-77 were cancelled, and Claims 73 and 78 were amended in the Response of 4/16/10.

3. Claims 1-11 and 13-64 are withdrawn from examination.

4. Claims 73 and 78 are all the pending claims under examination for this application.

5. Applicants amendments to the claims have necessitated new grounds for rejection. This Office Action is final.

Information Disclosure Statement

6. The IDS of 6/14/10 has been considered and entered. The initialed and signed 1449 form is attached.

Withdrawal of Rejections

Claim Rejections - 35 USC § 103

7. The rejection of Claims 12, 71, 72 and 77 under 35 U.S.C. 103(a) as being unpatentable over Long et al (Can. Res. 60:6630-6640 (2000); cited in the PTO 892 form of 5/15/07) in view of Culig et al. ((Br. J. Can. 81:242-251 (1999); cited in the PTO 892 form of 1/12/07) and Haapala et al., Lab. Invest., 81: 1647-1651, 2001); cited in the IDS of 12/2/04) is moot for the cancelled claims in the Response of 4/16/10.

8. The rejection of Claims 12, 71, 72 and 77 under 35 U.S.C. 103(a) as being unpatentable over Taplin et al. (Cancer Research, (1999), pp. 2511-2515, Vol. 59, No. 11; cited in the IDS of 12/2/04) in view of Joly-Pharaboz et al (J. Steroid Biochem. Molec. Biol. 55:67-76 (1995); cited in the PTO 892 form of 5/15/07) and further in view of Culig et al. ((Br. J. Can. 81:242-251 (1999); cited in the PTO 892 form of 1/12/07) and Haapala et al., Lab. Invest., 81: 1647-1651, 2001); cited in the IDS of 12/2/04) is moot for the cancelled claims in the Response of 4/16/10.

9. The rejection of Claims 12, 71, 72 and 77 under 35 U.S.C. 102(b) [*103(a)*] as being anticipated by Foury et al (J. Steroid Biochem. Molec. Biol. 66:235-240 (1998); cited in the PTO 892 form of 5/15/07) in view of Culig et al. ((Br. J. Can. 81:242-251 (1999); cited in the PTO 892 form of 1/12/07) and Haapala et al., Lab. Invest., 81: 1647-1651, 2001); cited in the IDS of 12/2/04) is moot for the cancelled claims in the Response of 4/16/10.

Rejections Maintained

Claim Rejections - 35 USC § 112, first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Enablement

10. The rejection of Claims 73 and 78 under 35 U.S.C. 112, first paragraph, because the specification does not reasonably provide enablement for culturing the instant claimed cells and test compound for an indefinite of undefined amount of time in order to identify a test compound that does not induce antiandrogen drug resistant cell population is maintained.

The rejection was set forth in the Office Action of 3/10/09 as follows:

"Nature of the Invention/ Skill in the Art

The claims are interpreted as being drawn to a method for identifying antiandrogen drugs that would prevent proliferation of any cancer cell comprising mutations in the androgen receptor where the cancer cell comprises a leucine or cysteine substitution for tryptophan at amino acid number 746 of SEQ ID NO:2 (Claim 73) or a sequence comprising "an alanine substitution for threonine at amino acid number 882 of SEQ ID NO:2" (Claim 74), and the cancer cells are human (Claim 75) and the human cancer cells are prostate cancer cells (Claim 76).

Essentially, the mutations in the AR of Claim 73 are induced by bicalutamide as taught by Applicants in Example 1, and the mutations in AR of Claim 74 are induced by flutamide, and therefore at least with respect to the starting population of cancer cells in the assay method, they are bicalutamide-resistant or refractory to bicalutamide and/or flutaminde resistant or refractory to flutaminde.

The relative skill in the art is a drug discovery technologist with a background in screening anti-hormone response drug therapy for cancer.

Disclosure in the Specification

The specification discloses that bicalutamide-resistant cancer cell lines comprising a leucine substitution for tryptophan at amino acid number 746 of SEQ ID NO:2 (LNCaP-cxD 11) or a sequence comprising an or cysteine substitution for tryptophan at amino acid number 746 of SEQ ID NO:2 (LNCaP-cxD2) were generated under long-term culture conditions in Example 1, namely, for 6 weeks or 13 weeks or more.

Prior Art Status: antiandrogen drug resistance occurs after long-term exposure to an antiandrogen and the mutations are drug-dependent

Some clinical findings have been reported concerning the relationship between cancer relapse after antiandrogen drug administration and AR (androgen receptor) mutations. AR mutations were observed in 5 of 17 patients who experienced relapsed prostate cancer after an endocrine therapy with a combination of flutamide and castration, all of which mutations were missense mutations of the 877th amino acid (corresponding to amino acid number 882 in the amino acid sequence of SEQ ID NO: 2) (Taplin et al., Cancer Res., 59:2511-2515, 1999); cited in the IDS of 12/2/04). On this type of mutant ARs, some antiandrogen drugs, including flutamide, conversely exhibited an action to stimulate cancer cell proliferation (Veldscholte et al., Biochem. Biophys. Res. Commun., 173: 534-540, 1990); cited in the IDS of 12/2/04). Also, although missense mutations of AR were identified in 3 of 11 biopsy samples from patients who experienced relapsed prostate cancer after an endocrine therapy with a combination of bicalutamide and surgical castration, all mutation sites were other than the 877th amino acid, which is a prevalent mutation site in flutamide-resistant relapsed cancers (Haapala et al., Lab. Invest., 81: 1647-1651, 2001); cited in the IDS of 12/2/04). Here Haapala states "Our data does not confirm the accumulation of AR mutations at the codon 877 reported by Taplin et al (1999), which is most likely due to the different anti- androgen used (bicalutamide versus flutamide) in the present study. This observation indicates that different types of AR variants are developed and selected for during bicalutamide and flutamide treatments and supports the data by Han et al (J. Biol. Chem 276:11204-11213 (2001)), who suggested that changes in the hormonal environment may drive the selection of spontaneous somatic mutations that provide a growth advantage for prostate cancer (CaP)." Notable amongst all of these studies is the time lapse for the treatment period in therapy response, so Taplin teaches 20 months; and Haapala teaches at least 11 months of treatment (see Table 1). Culig et al. (Br. J. Can. 81:242-251 (1999); cited in the PTO 892 form of 1/12/07) teaches that bicalutamide –resistant cancer growth starts to appear in vivo in xenografted prostate cancer cells in mice at around 35 days (or 5 weeks) with bicalutamide treatment (see Figure 7).

Undue Experimentation and Unpredictability

The instant claims are not limited to the culture period for observing whether development of drug-resistant cancer cells would occur under the culture conditions of the method. Thus depending on the antiandrogren drug

being tested much less the cell line standarized for the assay method, the ordinary artisan would not have been enabled to practice the method of the instant scope on cancer cell expressing the androgen mutations as claimed much less under culture conditions for an indeterminate and unclaimed amount of time in order to select a drug candidate that does not result in the proliferation of the cancer cell line.

The rejection was maintained in the Office Action of 11/16/09 as follows:

"Applicants' comments on pp. 13-14 of the Response of 7/1/09 are acknowledged and are not found persuasive. Applicants have amended claim 73 to insert the time period for incubation to be "at least 6 weeks." New Claim 78 recites the culture time period for at least 13 weeks.

Response to Arguments

This does not satisfy all grounds for rejection which addressed the lack of enablement for screening any genus of cancer cells expressing a leucine or cysteine substitution for tryptophan at amino acid number 746 of SEQ ID NO:2 or an alanine substitution for threonine at amino acid number 882 of SEQ ID NO:2.

The only cell line demonstrated to generate the specific mutations is the human prostate carcinoma cell line, LNCaP-FGC (ATCC Number: CRL-1740). The specification and the prior art are not enabling for producing a genus of cancer cell lines expressing a single claimed mutation much less any cancer cell line expressing both claimed mutations, and which can be used in the method assay in order to determine the cell line's sensitivity to just any test compound. Applicants have not explained which other cancer cell lines contain the mutations or how they can be induced to express the mutations but for the LNCaP-FGC parent cell line."

Applicants' allegations on pp. 12-14 of the Response of 4/16/10 have been considered and are not found persuasive.

A) Applicants allege "pending claims 73 and 78 have been amended to the use of LNCaP-FGC cells". Applicants allege the claims have been further amended to indicate that suppression of proliferation for 6 weeks or 13 weeks is an indication that the compound does not induce antiandrogen drug resistance.

Response to Arguments

The examiner submits that the method is not enabled to be practiced because the LNCaP-FGC cell line does not possess the instant claimed mutations in the AR gene as presently claimed. Applicants specification teaches that the LNCaP-FGC cell line was a starting population and an out-growth of which was the autonomously proliferating LNCaP- cxD11 and LNCaP-cxD2 cell lines, respectively, after culturing for 6-13 weeks in the presence of bicalutamide. Applicants next treated LNCaP- cxD11 and

LNCaP-cxD2 with bicalutamide in vitro and then the AR gene was sequenced. Applicants found codon 741 was mutated to TTG (leucine) and TGT (cysteine) in LNCaP- cxD 11 and LNCaP-cxD2, respectively. Thus, it is incorrect that the starting LNCaP-FGC cell line inherently possesses the instant claimed AR mutations found in SEQ ID NO:2. The ordinary artisan could not predict how to generate and maintain the instant AR mutations in the founding or parental LNCaP-FGC cell line absent undue experimentation. Also, it is not clear that the ordinary artisan could reproducibly generate the same mutations in the same gene for the same starting cell line using bicalutamide under any culture conditions. "[T]o be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation.'" *Genentech, Inc. v. Novo Nordisk*, A/S, 108 F.3d 1361, 1365 (Fed. Cir. 1997) (quoting *In re Wright*, 999 F.2d 1557, 1561 (Fed. Cir. 1993)).

The rejection is maintained.

New Grounds for Rejection

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Biological Deposit

11. Claims 73 and 78 are rejected under 35 U.S.C. § 112, first paragraph, because

the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention, because the specification does not provide evidence that the claimed biological materials are (a) known and readily available to the public; (b) reproducible from the written description.

It is unclear if a cell line having the exact chemical identity of the AR-mutated LNCaP-FGC comprising a leucine or cysteine substitution for tryptophan at amino acid number 746 of SEQ ID NO:2 is known and publicly available, or can be reproducibly isolated without undue experimentation. Therefore, a suitable deposit for patent purposes is suggested. Without a publicly available deposit of the above cell line, one of ordinary skill in the art could not be assured of the ability to practice the invention as claimed. Exact replication of: (1) the claimed cell line; and/or (2) a cell line which comprising the chemically and functionally distinct SEQ ID NO:2 claimed. Therefore, it would require undue experimentation to reproduce the claimed cell line. Deposit of the AR-mutated LNCaP-FGC cell line would satisfy the enablement requirements of 35 U.S.C. § 112, first paragraph. See, 37 C.F.R. 1.801-1.809.

If the deposit is made under the provisions of the Budapest Treaty, filing of an affidavit or declaration by applicant or assignees or a statement by an attorney of record who has authority and control over the conditions of deposit over his or her signature and registration number stating that the deposit has been accepted by an International Depository Authority under the provisions of the Budapest Treaty and that all restrictions upon public access to the deposited material will be irrevocably removed upon the grant of a patent on this application. This requirement is necessary when deposits are made

under the provisions of the Budapest Treaty as the Treaty leaves this specific matter to the discretion of each State.

If the deposit is not made under the provisions of the Budapest Treaty, then in order to certify that the deposits comply with the criteria set forth in 37 CFR 1.801-1.809 regarding availability and permanency of deposits, assurance of compliance is required. Such assurance may be in the form of an affidavit or declaration by applicants or assignees or in the form of a statement by an attorney of record who has the authority and control over the conditions of deposit over his or her signature and registration number averring:

(a) during the pendency of this application, access to the deposits will be afforded to the Commissioner upon request:

(b) all restrictions upon the availability to the public of the deposited biological material will be irrevocably removed upon the granting of a patent on this application:

(c) the deposits will be maintained in a public depository for a period of at least thirty years from the date of deposit or for the enforceable life of the patent of or for a period of five years after the date of the most recent request for the furnishing of a sample of the deposited biological material, whichever is longest; and

(d) the deposits will be replaced if they should become nonviable or non-replicable.

Amendment of the specification to recite the date of deposit and the complete name and address of the depository is required. As an additional means for completing the record, applicant may submit a copy of the contract with the depository for deposit

and maintenance of each deposit.

If a deposit is made after the effective filing date of the application for patent in the United States, a verified statement is required from a person in a position to corroborate that the biological material described in the specification as filed is the same as that deposited in the depository, stating that the deposited material is identical to the biological material described in the specification and was in the applicant's possession at the time the application was filed.

Applicant's attention is directed to In re Lundak, 773 F.2d. 1216, 227 USPQ 90 (CAFC 1985) and 37 CFR 1.801-1.809 for further information concerning deposit practice.

Written Description/ New Matter

12. Claims 73 and 78 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 73 and 78 are interpreted as being drawn to the method for identifying antiandrogen drugs using “LNCaP-FGC cells comprising a leucine or cysteine substitution for tryptophan at amino acid number 746 of SEQ ID NO:2”.

The examiner’s search of the specification for the limitation does not identify literal support for this limitation. The specification teaches codon 741 of the AR gene of

SEQ ID NO: 2 was mutated to TTG (leucine) and TGT (cysteine) in LNCaP- cxD 11 and LNCaP-cxD2, respectively.

MPEP 706.03(m) states in part "New matter includes not only the addition of wholly unsupported subject matter, but may also include adding specific percentages or compounds after a broader original disclosure, or even the omission of a step from a method. See MPEP § 608.04 to § 608.04(c). See In re Wertheim, 541 F.2d 257, 191 USPQ 90 (CCPA 1976) and MPEP § 2163.05 for guidance in determining whether the addition of specific percentages or compounds after a broader original disclosure constitutes new matter.")

This is a new matter rejection.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

13. Claims 73 and 78 are rejected under 35 U.S.C. 103(a) as being unpatentable over Soto et al. (USPN 6994992; published 2/7/06; filed 2/24/00) in view of Culig et al. ((Br. J. Can. 81:242-251 (1999); cited in the PTO 892 form of 1/12/07) and Haapala et al., Lab. Invest., 81 1647-1651,2001); cited in the IDS of 12/2/04).

Claims 73 and 78 are interpreted as being drawn to the method for identifying antiandrogen drugs using LNCaP-FGC cells comprising a leucine or cysteine substitution for tryptophan at amino acid number 746 of SEQ ID NO:2 where an antiandrogen identified by the method suppresses proliferation for 6 weeks (Claim 73) or 13 weeks (Claim 78).

The claimed invention was prima facie obvious over Soto in view of Culig and Happala at the time of the invention.

Soto teaches in some patients with metastatic disease of the prostate, hormone therapy (e.g., antiandrogen) is frequently used. However, many patients on hormone therapy develop hormone resistance which is problem in managing hormone refractive disease. Thus an objective of Soto is to identify compounds that suppress these latent, antiandrogen-resistant cells. Soto teaches methods for identifying compounds that achieve this end using LNCaP-FGC cells and culturing for extended periods of time . The claimed LNCaP-FGC cells appears to be the same as the prior art cells, absent a showing of unobvious differences. The office does not have the facilities and resources to provide the factual evidence needed in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is on the

applicant to prove that the claimed product is different from those taught by the prior art and to establish patentable differences. See In re Best 562F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray 10 USPQ 2d 1922 (PTO Bd. Pat. App. & Int. 1989). Soto does not culturing for 6 weeks or 13 weeks to observe the anti-proliferatve effects of the test drug whereas does Culig and Happala.

Culig teaches anti-androgen withdrawal phenomenon may be in part attributed to mutant ARs detected in prostatic carcinomas. Culig teaches that bicalutamide –resistant cancer growth starts to appear in vivo in xenografted prostate cancer cells in mice at around 40 days (or 5.7 weeks) (see Figure 6 and 7) and experiments extending to 65 days (9 weeks) (see Figure 6). Thus Culig at least suggests that bicalutamide – resistance in prostate cancer cells is observable at at least 6 weeks.

Haapala teaches the observation of AR mutations occurring at at least 11 months (at least 6 weeks or at least 13 weeks) of bicalutamide treatment (see Table 1).

One skilled in the art would have been motivated to have produced the drug screening method and been reasonably assured of success at the time the invention was made based on the combined disclosure of Soto, Culig and Haapala. The concept of selecting drugs that do not induce androgen resistant cancer cell lines (with or without mutated ARs) over long-term exposure was well understood within the field of art at the time of the invention based on the disclosures of Soto, Culig and Haapala. Modifying the assay methods of Soto to include incubating the prostate cancer cells in the presence of the test drug for at least 6 or 13 weeks in order to ensure that the cancer cells do not proliferate, or that a population of cells do not become drug-

resistant or tolerant, would have been obvious to the ordinary artisan in considering the long-terms effects observed for art-known antiandrogen drugs where such resistance had been observed in vivo. Thus the motivation would have been to develop an assay method that considered screening for drug resistance developing at at least 6 weeks or at at least 13 weeks of drug exposure for any new candidate because of the art-recognized phenomenon for this class of drugs. The ordinary artisan would have been reasonably assured of success in having produced the claimed assay method because the material reagents were available, the establishment of drug screening assay for AR was already established by the three references alone and in combination and to change the culture period to ensure that a drug-resistant population of cancer cells taught by Soto did not develop or escape detection by short term culturing, the artisan would have been motivated to culture and/or observe for longer periods, i.e., 6 weeks or 13 weeks.

14. Claims 73 and 78 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zhao et al. (Urol. Res. 20(3):193-197 (1992); Abstract only) in view of Culig et al. ((Br. J. Can. 81:242-251 (1999); cited in the PTO 892 form of 1/12/07) and Haapala et al., Lab. Invest., 81 1647-1651,2001); cited in the IDS of 12/2/04).

The interpretation of Claims 73 and 78 is discussed above.

The claimed invention was prima facie obvious over Zhao in view of Culig and Happala at the time of the invention.

Zhao teaches screening the LNCaP-FGC cell line proliferation for responsivity to TNF. The claimed LNCaP-FGC cells appears to be the same as the prior art cells, absent a showing of unobvious differences. The office does not have the facilities and resources to provide the factual evidence needed in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is on the applicant to prove that the claimed product is different from those taught by the prior art and to establish patentable differences. See In re Best 562F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray 10 USPQ 2d 1922 (PTO Bd. Pat. App. & Int. 1989). Zhao does not teach culturing for 6 weeks or 13 weeks to observe the anti-proliferatve effects of the test drug whereas does Culig and Happala.

Culig teaches anti-androgen withdrawal phenomenon may be in part attributed to mutant ARs detected in prostatic carcinomas. Culig teaches that bicalutamide –resistant cancer growth starts to appear in vivo in xenografted prostate cancer cells in mice at around 40 days (or 5.7 weeks) (see Figure 6 and 7) and experiments extending to 65 days (9 weeks) (see Figure 6). Thus Culig at least suggests that bicalutamide – resistance in prostate cancer cells is observable at at least 6 weeks.

Haapala teaches the observation of AR mutations occurring at at least 11 months (at least 6 weeks or at least 13 weeks) of bicalutamide treatment (see Table 1).

One skilled in the art would have been motivated to have produced the drug screening method and been reasonably assured of success at the time the invention was made based on the combined disclosure of Zhao, Culig and Haapala. The concept

of selecting drugs that do not induce androgen resistant cancer cell lines (with or without mutated ARs) over long-term exposure was well understood within the field of art at the time of the invention based on the disclosures of Zhao, Culig and Haapala. Modifying the assay methods of Zhao to include incubating the prostate cancer cells in the presence of the test drug for at least 6 or 13 weeks in order to ensure that the cancer cells do not proliferate, or that a population of cells do not become drug-resistant or tolerant, would have been obvious to the ordinary artisan in considering the long-terms effects observed for art-known antiandrogen drugs where such resistance had been observed in vivo. Thus the motivation would have been to develop an assay method that considered screening for drug resistance developing at at least 6 weeks or at at least 13 weeks of drug exposure for any new candidate because of the art-recognized phenomenon for this class of drugs. The ordinary artisan would have been reasonably assured of success in having produced the claimed assay method because the material reagents were available, the establishment of drug screening assay for AR was already established by the three references alone and in combination and to change the culture period to ensure that a drug-resistant population of cancer cells taught by Zhao did not develop or escape detection by short term culturing, the artisan would have been motivated to culture and/or observe for longer periods, i.e., 6 weeks or 13 weeks.

Conclusion

15. No claims are allowed.

16. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lynn Bristol whose telephone number is 571-272-6883. The examiner can normally be reached on 8:00-4:00, Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Lynn A. Bristol/
Primary Examiner, Art Unit 1643